REMARKS

Claims 1-81 were pending in the application.

Claims 1-29 and 36-81 have been withdrawn from consideration as directed to non-elected inventions

Upon entry of this amendment claims 32-35 will be pending.

No new matter has been added.

Claim Rejections 35 USC § § 101, 112 First Paragraph–Utility

The Examiner has rejected claims 30-35, under 35 USC § 101 alleging that they are drawn to an invention with no apparent or disclosed patentable utility. First, the Examiner asserts that the polypeptide has been assigned a function because of its similarity to known proteins and then alleges that "it is commonly known in the art that sequence-to-function methods of assigning protein function are prone to error" citing Doerks, et al 1998, Brenner 1999 and Bork et al 1996.

The Examiner then goes on to state that even if *arguendo*, the nucleic acid encoding nGPCR-14 is found to be a G protein coupled receptor "its function is unknown" and that

> "Until some actual and specific significance can be attributed to the protein identified in the specification as nGPCR-14, the instant invention is incomplete. The polypeptide encoded by the nucleic acids of the invention is known to be structurally analogous to proteins that are known in the art as G protein coupled receptors. In the absence of knowledge of the natural substrate or biological significance of this protein, the is no immediately obvious patentable use for it."

The Applicants disagree.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 (and 112) of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," Anderson v. Natta, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. Brenner v. Manson, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See Brenner v. Manson, 383 U.S. 519, 534 [148 USPQ 689] (1966); Brookiree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally

> incapable of achieving a useful result"); Fuller v. Berger, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end"). Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In Stiftung v. Renishaw PLC, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." Envirotech Corp. v. Al George, Inc., 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).
>
> The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill' in the art would understand how to use the claimed invention, it is sufficiently specific. See Standard Oil Co. v. Montedison, S.p.a., 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. Cross v. lizuka, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." Brenner, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. Nelson v. Bowler, 626 F.2d 853, 856,206 USPQ 881 (CCPA 1980). As demonstrated in the Juicy Whip and Brooktree cases, supra, a mere "identifiable" benefit is substantial. So long as the claimed invention is not totally incapable of achieving a useful result, it meets the "substantiality" requirement. Ids.

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any separate showing to demonstrate utility, regardless of what is disclosed in the patent specification. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. Id.

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. In re Cortright, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); In re Brana, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. Id. To do so, the Patent Office must provide evidence or sound scientific reasoning. See In re Langer, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. Brana, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. Brenner, 383 U.S. at 532.

II. The Examiner has misstated the Art as to Predictability of Associating Sequence with Function

As noted above the Examiner cites literature identifying some of the difficulties that may be involved in predicting protein function, none of the cited references suggests that functional homology cannot be inferred by a reasonable probability in any particular case. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et al., Proc. Natl. Acad. Sci. 95:6073-78 (1998) (**Exhibit 1**). Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the polypeptide encoded for by our claimed polynucleotides is related to the reference polypeptides is, accordingly, very high. None of the Examiner's cited references contradicts Brenner's basic rule Nor do they contradict our additional evidence of similarity to the G-protein coupled receptors, e.g., with respect to the presence of clearly delineated 7 transmembrane domains and conserved cysteine residues in the extracellular loops. At most, these articles cited by the USPTO individually and together stand for the proposition that it is difficult to make predictions about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability as noted in the section above.

Under the Patent Law, the USPTO must accept the applicant's demonstration that the polypeptide encoded by the claimed invention is a member of a particular protein family and that

utility is proven by a reasonable probability unless the USPTO can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt the asserted utility. See In re Langer, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has simply not provided sufficient evidence or sound scientific reasoning to the contrary.

The Rejection Under 35 U.S.C. §101 Should be Withdrawn.

The Examiner has rejected claims 32-35, alleging that the claimed invention is not supported by a specific and substantial asserted utility or a well-established utility. The Applicants respectfully traverse this rejection.

A. GPCR proteins have a well established utility.

Many medically significant biological processes are mediated by signal transduction pathways involving G-proteins and other second messengers, and G protein coupled seven transmembrane receptor proteins are recognized as important therapeutic targets for a wide range of diseases. According to a recently issued United States patent, nearly 350 therapeutic agents targeting GPCRs have been successfully introduced onto the market in only the last fifteen years. **(See U.S. Patent No. 6,114,127, at col. 2, lines 45-50.)** A recent journal review reported that most GPCR ligands are small and can be mimicked or blocked with synthetic analogues. That, together with the knowledge that numerous GPCRs are targets of important drugs in use today, make identification of GPCRs "a task of prime importance." **(See Exhibit 2**, Marchese et al., Trends Pharmacol. Sci., 20(9): 370-5., 1999.) Thus, the allegations that there is no well established utility for proteins of the class that the Applicants are now claiming is directly refuted by industry evidence. In this respect, the G protein coupled receptor family is analogous to the chemical genus that was the subject of In re Folkers, 145 USPQ 390 (CCPA 1965) (Compound that belongs to class of compounds, members of which are recognized as useful, is considered useful under §101.) The Patent Office does not serve the public by attempting to substitute a formulaic analysis of § 101 for the established judgment of the biopharmaceutical industry as to what is "useful." If the Patent Office is aware of any literature from the industry suggesting that GPCR's are not useful, the Applicants request that it be made of record.

Applicants would note for the record that the patent office apparently agrees with Applicant's reasoning in that it has granted and apparently continues to grant patents to G-protein coupled receptors, their encoding polynucleotides and antibodies directed to them in

which no natural substrate/ligand or specific biological significance is ascribed to the protein.

Specifically, Applicants would like to bring the following US Patents to the Examiner's attention:

US Patent 6,518,414 Maclennan "Molecular Cloning and Expression of G-Protein Coupled Receptors" (Claims an isolated polynucleotide)
US Patent 6,511,826 Li et al. "Polynucleotides Encoding Human G-Protein Chemokine Receptor (CCR5) HDGNR10" (Claims an isolated polynucleotide encoding a protein identified as a "chemokine receptor" with no specific chemokine identified)
US Patent 6,372,891 Soppet et al. "Human G-Protein Receptor HPRAJ70" (Claims an antibody directed to a G-protein coupled receptor)
US Patent 6,361,967 Agarwal et al. "AXOR10, A G-Protein Coupled Receptor" (Claims an isolated polynucleotide)
US Patent 6,348,574 Godiska et al. "Seven Transmembrane Receptors" (Claims an antibody directed to a G-protein coupled receptor)
US Patent 6,114,139 Hinuma et al. "G-Protein Coupled Receptor Protein and A DNA Encoding the Receptor" (Claims an isolated polynucleotide) Describe below.
US Patent 6,111,076 Fukusumi et al. "Human G-Protein Coupled Receptor (HIBCD07)" (Claims isolated polypeptide)
US Patent 6,107,475 Godiska et al. "Seven Transmembrane Receptors" (Claims isolated polynucleotide and methods)
US Patent 6, 096,868 Halsey et al. "ECR 673: A 7-Transmembrane G-Protein Coupled Receptor" (Claims isolated polypeptide)
US Patent 6,090,575 Li et al. "Polynucleotides Encoding Human G-Protein Coupled Receptor GPR1" (Claims isolated polynucleotide)
US Patent 6,071,722 Elshourbagy et al. "Nucleic Acids Encoding A G-Protein Coupled 7TM Receptor (AXOR-1)" (Claims an isolated polynucleotide)
US Patent 6, 071,719 Halsey et al. "DNA Encoding ECR 673: A 7-Transmembrane G-Protein Coupled Receptor" (Claims an isolated polynucleotide)
US Patent 6,060,272 Li et al. "Human G-Protein Coupled Receptors" (Claims isolated polynucleotide)
US Patent 6,048,711 Hinuma et al. "Human G-Protein Coupled Receptor Polynucleotides" (Claims isolated polynucleotide)
US Patent 6,030,804 Soppet et al. "Polynucleotides Encoding G-Protein Parathyroid Hormone Receptor HLTDG74 Polypeptides" (Claims isolated polynucleotide)
US Patent 6,025,154 Li et al. "Polynucleotides Encoding Human G-Protein Chemokine Receptor HDGNR10" (Claims an isolated polynucleotide encoding a protein identified as a "chemokine receptor" with no specific chemokine identified)
US Patent 5,998,164 Li et al. "Polynucleotides Encoding Human G-Protein Coupled Receptor GPRZ" (Claims isolated polynucleotide)
US Patent 5,994,097 Lal et al. "Polynucleotide Encoding Human G-Protein Coupled Receptor" (Claims isolated polynucleotide)
US Patent 5,958,729 Soppet et al. "Human G-Protein Receptor HCEGH45" (Claims isolated polypeptide)

US Patent 5,955,309 Ellis et al. "Polynucleotide Encoding G-Protein Coupled Receptor (H7TBA62)" (Claims isolated polynucleotide)
US Patent 5,948,890 Soppet et al. "Human G-Protein Receptor HPRAJ70" (Claims isolated polypeptide)
US Patent 5, 945,307 Glucksmann et al. "Isolated Nucleic Acid Molecules Encoding A G-Protein Coupled Receptor Showing Homology to The 5HT Family of Receptors" (Claims isolated polynucleotide)
US Patent 5, 942,414 Li et al. Polynucleotides Encoding Human G-Protein Coupled Receptor HIBEF51" (Claims isolated polynucleotide)
US Patent 5, 912,335 Bergsma et al. "G-Protein Coupled Receptor HUVCT36" (Claims isolated polynucleotide)
US Patent 5,874,245 Fukusumi et al. "Human G-Protein Coupled Receptors (HIBCD07)" (Claims isolated polynucleotide)
US Patent 5,871,967 Shabon et al. "Cloning of A Novel G-Protein Coupled 7TM Receptor" (Claims isolated polynucleotide)
US Patent 5,869,632 Soppet et al. "Human G-Protein Receptor HCEGH45" (Claims isolated polynucleotide)
US Patent 5,856,443 MacLennan et al. "Molecular Cloning and Expression of G-Protein Coupled Receptors" (Claims isolated polynucleotide)
US Patent 5,834,587 Chan et al. "G-Protein Coupled Receptor, HLTEX11" (Claims isolated polypeptide)
US Patent 5,776,729 Soppet et al. "Human G-Protein Receptor HGBER32" (Claims isolated polynucleotide)
US Patent 5,763,218 Fujii et al. "Nucleic Acid Encoding Novel Human G-Protein Coupled Receptors" (Claims isolated polynucleotide)
US Patent 5,756, 309 Soppet et al. "Nucleic Acid Encoding A Human G-Protein Receptor HPRAJ70 and Method of Producing the Receptor" (Claims isolated polynucleotide)
US Patent 5,585,476 MacLennan "Molecular Cloning and Expression of G-Protein Coupled Receptors" (Claims isolated polynucleotide)
US Patent 5,759,804 Godiska et al. "Isolated Nucleic Acid Encoding Seven Transmembrane Receptors" (Claims isolated polynucleotide and methods)

Applicants would submit these issued US Patents are evidence of an art recognized utility for G-protein coupled receptors whose natural ligand is unknown. If the Patent Office would take the position that issued patents are not sufficient evidence of art recognition then Applicants respectfully request that this position be made of record. In the alternative, if the Patent Office wishes to take the position that these issued patents are directed to non-statutory subject matter, then Applicants respectfully request that this position be made of record as well.

The use of the nGPCR-14 polypeptide (SEQ ID NO: 86) to screen for ligands that activate or inhibit nGPCR-14 is a specific and substantial utility. The use of a particular receptor such as nGPCR-14 to identify materials which specifically bind to that receptor is a specific utility because the method is not applicable to the general class of receptors. The method (which uses nGPCR-14 as a reagent) only identifies binding compounds for nGPCR-14, and cannot be expected to identify compounds that bind any other receptor. Stated differently, the identification of ligands which specifically bind to nGPCR-14 cannot be carried out with any integral membrane protein as asserted by the Examiner, but rather can only be carried out with nGPCR-14, if one hopes to have any reasonable expectation of success. The family of GPCRs is large, and the use of any other GPCR would not be expected to identify a ligand for nGPCR-14. Thus, a "specific" utility exists for nGPCR-14 polypeptides.

The identification of ligands which specifically bind nGPCR-14 is a substantial utility. As explained in part A, above, the reported track record of successes in the pharmaceutical industry at targeting GPCR's (almost 350 marketed therapeutics in 15 years) supports a conclusion that such utility is substantial and credible.

III. The Rejection Under 35 U.S.C. §112, First Paragraph for Lack of Utility Should be Withdrawn.

In the Office Action, the Patent Office rejected claims 1-35, 77 and 80-85 alleging that the claimed invention is not supported by a specific and substantial or a well established utility. In support of the rejection, the Examiner relied on the utility rejection "set forth above." The Applicants respectfully traverse this rejection, for the reasons set forth above related to the utility rejection.

IV. The Rejection Under 35 U.S.C. §112, First Paragraph for Lack of Enablement Should be Withdrawn.

Claims 30 and 31 have been cancelled to facilitate prosecution and render the Examiner's rejection moot as to those claims. Applicants reserve the right to present these claims in a later filed application.

Applicants respectfully disagree with the Examiner's apparent contention that the to be entitled to claims reading sequences other than SEQ ID NO:192 that they are required to disclose within the specification amino acid residues to be modified to an extent more than they

have already done so through the disclosure of the sequences in the application. The Applicants would point the Examiner to *In re Angstad*, 190 USPQ 214, (C.C.P.A. 1976)

> We cannot agree with the board that appellants' disclosure is not sufficient to enable one of ordinary skill in the art to practice the invention without undue experimentation. .... The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments whichare expressly disclosed.

The question is not, as noted in *Angstad*, whether Applicant's have disclosed each and every embodiment of their invention covered by a claim but whether they have enabled one of ordinary skill to make and use their invention. Applicant's assert unequivocally that they have. The question is not, as the Examiner would have it, whether "additional assays or screens are required to isolate sequences within the scope of the claim but whether such additional assays constitute *undue* experimentation. The Federal Circuit has specifically validated the proposition that a disclosure that utilizes routine screening using well know procedures to make the invention constitutes an enabling disclosure.

> With respect to screening, the only permissible view of the evidence is that screening methods used to identify the necessary characteristics, including affinity, of the monoclonal antibodies used in the invention were known in the art and that the '110 patent contemplated one of those. At trial, Monoclonal's counsel stated "it is a procedure that was known in '78." . . . . We hold as a matter of law that the '110 patent disclosure is enabling.
> Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 U.S.P.Q. (BNA) 81 (Fed. Cir. 1986)

To the nature of the experimentation required to make Applicant's invention is so old as to be categorized as routine. The techniques of site directed and random mutagenesis, DNA sequencing, and hybridization were well known in 1983 (Zoller and Smith (1983) Methods in Enzymology, Volume 100, 468-500 **Exhibit 3**)). Almost 18 years later by the time of Applicant's filing in 2001, mutagenesis of DNA of cloned sequences was so routine as to be

accomplished via readily obtainable kits. [1997 Pharmacia Biotech Catalog, pgs 173-174, U.S.E. Mutagenesis Kit, **Exhibit 4**)

If the Examiner is aware of *Hybritech* being overuled or in some way only applying to the field of monoclonal antibodies, Applicants respectfully request that the Examiner make such authority of record in this case.

Applicants would also point the Examiner to *In re Wands*, 858 F. 2d at 737, 8 U.S.P.Q.2d at 1404 and would assert that the teachings of Wands dictate a finding that the amount of experimentation required to practice the entire scope of the Applicant's invention is not undue. That is, Applicants believe that their disclosure provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time of filing the application and all of the methods needed to practice the invention were well known and so simple as to be reduced to kit form.

IV. The Rejection Under 35 U.S.C. §112, First Paragraph and Second Paragraph for Lack of Written Description and Indefiniteness Should be Withdrawn.

Claims 30 and 31 have been cancelled and claims 32-35 amended to facilitate prosecution and render the Examiner's rejection moot as to those claims. Applicants reserve the right to present these claims in a later filed application.

The pending claims specifically make reference to a percentage of homology and therefore recite more than sufficient structure to render the Examiner's rejection moot.

V. The Rejection under 35 U.S.C. §102 should be withdrawn

The Examiner has rejected the pending claims as being anticipated by Cserjesi et al (1995). Claims 30 and 31 have been cancelled and claims 32-35 amended to facilitate prosecution and render the Examiner's rejection moot as to those claims. Applicants reserve the right to present these claims in a later filed application.

VI. Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

Respectfully submitted,

Edward F. Rehberg

Date: 1-29-04

Edward F. Rehberg, Attorney
Registration No. 34,703

Pharmacia & Upjohn Company
Global Intellectual Property
301 Henrietta Street
Kalamazoo, Michigan 49001

Telephone No. (269) 833-7829 or (269) 833-9500
Telefax No. (269) 833-8897 or (269) 833-2316